

REMARKS

A paragraph has been added to reflect government support during invention by a previously omitted inventor, whose conception of a portion of the invention occurred during employment by the Department of Energy. The Department of Energy declined to pursue the invention.

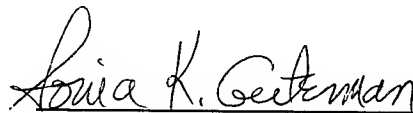
Applicants have further amended the specification to correct clerical errors. No new matter has been added by this amendment.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact of the undersigned at the telephone number provided below.

It is believed that no fee is due with this amendment. Please charge any fee that may be due to Deposit Account No. 50-0311, Reference no. 24499-530.

Respectfully submitted,



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Version with Markings to Show Changes Made

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Government Funding

A portion of the invention was made with funding from the Department of Energy. The government has certain rights in the invention.

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Fig. 1 is a graphical illustration showing a [bottom] top view of an apparatus for performing microfluidic analysis in accordance with an embodiment of the invention;

Fig. 2 is a graphical illustration showing a [top] bottom view of the apparatus of Fig.1;

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Fig. 1 is a graphical illustration showing a [bottom] top view of an apparatus for performing microfluidic analysis in accordance with an embodiment of the invention. The apparatus includes a three dimensional [a] housing **150** having a plurality of fluid lines **141-148**. The fluid lines **141-148** are disposed within the housing in at least two layers such that some fluid lines are closer to a top face of the housing **155** and others are closer to a bottom face of the housing **156**, shown in Fig. 2. Each of the fluid lines has an inlet **131-138** for receiving a fluid from a fluid pump or other fluid delivery apparatus. Such a fluid pump may be external to the housing **150** or it may be part of the housing so as to create a completely self-contained unit. The housing **150** also includes a plurality of control lines **111-120** in communication with valves **161-170**. Valves **161-166** are in communication with the fluid lines **141-148**. Each of the control lines **111-120** receives a control fluid, such as a gas or other fluid, from an inlet **101-110**. The fluid lines **141-148**, control lines **111-120** and fluid paths (discussed below) may be 0.5 mm in diameter. For example, the diameter of the lines and paths may range from

about 0.05 mm to about 0.6 mm. In accordance with further embodiments of the invention, the diameter of the lines and paths may be about 0.05 mm to about 0.2 mm; from about 0.1 mm to about 0.3 mm; and from about 0.2 mm to about 0.6 mm. Control fluid and other fluids may be provided to the apparatus through the use of a robotic device, or may be provided manually.

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The valves 161-170 may be pneumatic valves that are activated by the control fluid. In the embodiments of Figs. 1-14, the control fluid, when pressurized, serves to close the valves 161-170. In Fig. 1 the control fluid has not been pressurized, thus the valves are all open, whereas in Fig. 3, the control fluid is pressurized and the valves 161-170 are closed. When the control fluid is a high density gas, such as air, the response time of the valves quickens. The number of valves in the apparatus may be less than, more than or equal to the number of fluid lines. Similarly, the number of valves may be less than, equal to or more than the number of control lines.

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Coating of micromechanical sensors with various interactive molecules is described in U.S. patent number 6,118,124, issued September 12, 2000. A coating material is deposited on a microcantilever by depositing a metal which may be selected from at least one of the group consisting of aluminum, copper, gold, chromium, titanium, and silver[, and mercury]. Further, a plurality of metals may be deposited on a microcantilever by depositing, for example, a first layer of chromium and a second layer of gold, or a first layer of titanium and a second layer of gold. Coatings may be amalgams or alloys comprising a plurality of metals.

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The apparatus of Figs. 1 and 2 may be a card or cartridge consisting of about 17 layers of one or more plastic polymers. Such cards and cartridges may be custom manufactured, for example, by Micronics, Inc. of Redmond, Washington. These cards or cartridges may be mounted in a manifold that receives fluid pump lines or fluid from other fluid delivery devices. Similarly, the pumps may be part of the card as mentioned above. The apparatus may also be mounted on a temperature-controlled platform. The apparatus may be used to identify a particular molecule in one or more sample fluids,

- as is shown in Figs. 3-14.

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Fig. 14 illustrates a way to provide the fourth interaction cell **181** with a fourth sample solution. Here, control lines **111** and **113** are de-pressurized, valves **161** and **167** are opened and the fourth sample solution flows from a fluid pump to fluid line **141** via inlet **131**. The fourth sample solution will flow into fluid path **746** and into expansion chamber **151**, and gas will be removed from the solution. The [third] fourth sample solution proceeds to the interaction cell **181** via fluid path **747** and inlet **171**. Outflow of the [third] fourth sample solution from the interaction cell **181** will flow into output line **175**, and the outflow will be stored in a waste receptacle (or reservoir for collection) via waste line **190** and waste outlet **191**.

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Fig. 15 is a graphical illustration showing an apparatus for performing microfluidic analysis in which the valves of the apparatus are normally closed in accordance with another embodiment of the invention. Unlike the embodiment of Fig. 1, in Fig. 15, all of the valves **1051-1058** and **1061-1064** are closed under normal atmospheric pressure [(when only air is in the lines)]. This configuration reduces the duty cycle of the electrical components of the system and minimizes the amount of

current needed to drive the system. However, whether the valves are open or closed under normal atmospheric conditions is purely arbitrary and each of the embodiments of Fig. 1 and Fig. 15 may operate either way with respect to the configuration of lines and valves. Additionally, in accordance with the embodiment of Fig. 15, the fluid lines **1011-1019** and fluid inlets **1001-1008** are at the top of the figure, rather than at the bottom as in Fig. 1.

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As was the case with the apparatus of Fig. 1, the embodiments of Fig. 15 may be in the form of a card or cartridge comprising one or more plastic polymers. Preparation fluids, such as linker, buffer, ligand solutions, and sample solutions may be input to the interaction cells **1021-1024** in a discriminatory manner. A buffer solution may be input to all of the cells or to a subset of the cells, for example, to three of the cells, two of the cells or only to one of the cells. Similarly, a different sample solution may be input to each of the cells, or to a subset of the cells.

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The ligand may be a biomaterial, for example, a protein such as an enzyme or a synthetic polypeptide, or it can be a nucleic acid such as RNA or DNA. A biomaterial that is a macromolecule may comprise all or a portion of a nucleic acid or a protein. The protein or polypeptide may comprise an epitope, an antibody, an antibody fragment, an enzyme, or any other embodiment of a molecule containing peptide bonds. The analyte to be detected or quantified in a sample may be a biomaterial such as a macromolecule, or an organic or inorganic small molecule. Similarly, the analyte may be a hormone, for example, the hormone may be a steroid for example, a sex steroid or glucocorticoid, or a polypeptide hormone such as a cytokine. Either of the ligand or the analyte may comprise all or a portion of an antibody or an antigenic material, or all or a portion of an enzyme.

Examples and methods for the use of the apparatus of the invention are shown in Table 1. In Example 1, the apparatuses of Figs. 3-19 is used to demonstrate a movement or deflection of a plurality of microcantilevers in a microcantilever array when a sample solution contains an analyte, such as a particular chemical or biological component, capable of binding to or interacting with a ligand affixed to a surface of the microcantilever. Cell A can be a reaction cell that provides a positive control; deflection of microcantilevers is caused by interaction on a surface of the cantilever of components of fluids sequentially provided to cell A. Cell B can be a reference cell; for example, a control buffer known to lack the analyte, is added to this cell instead of a sample. This control can determine the extent of microcantilever deflection that occurs as a result of interactions between preparation liquids such as a linker solution and an antibody solution, or other environmental forces. Cell C can be a negative control cell, for example, which has not been exposed to linker solution. Microcantilever deflection in this cell can determine the extent of ligand binding to a microcantilever surface density, in the absence of a [cross-linking] cross-linking agent. Cell D can be another control cell, containing for example, bovine serum albumin instead of the biomaterial of interest, so that microcantilever deflection is a measure of non-specific binding of the analyte.